New-Onset Type 2 Diabetes Mellitus Among Patients Receiving HIV Care At Newlands Clinic, Harare, Zimbabwe. A Retrospective Cohort Analysis

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Keywords: Type 2 Diabetes Mellitus, HIV Infection, Zimbabwe

*A*bstract

Background

Diagnosing and managing Type 2 Diabetes Mellitus (T2DM) among people living with HIV (PLHIV) is becoming more important as the HIV-infected population ages and becomes increasingly comorbid. Data on incidence of T2DM in PLHIV in Sub-Saharan Africa is scarce.

Methods

We analyzed data for all HIV-infected patients older than 16 years who attended Newlands Clinic between March 1, 2004 and April 29, 2015. The clinic considers patients whose random blood sugar is higher than 11.1 mmol/L and which is confirmed by a fasting blood sugar higher than 7.0 mmol/L to have T2DM. T2DM is also diagnosed in symptomatic patients who have a RBS >11.0 mmol/l. Risk factors for developing T2DM were identified using Cox proportional hazard models adjusted for confounding. Missing baseline BMI data were multiply imputed. Results are presented as adjusted hazard ratios (aHR) with 95% confidence intervals (95%CI).

Results

Data for 4,110 participants were included: 67.2% were women; median age was 37 (IQR:31-43) years. Median baseline CD4 count was 197 (IQR: 95-337) cells/mm^3. The proportion of participants with hypertension at baseline was 15.5% (n=638). Over a median follow-up time of 4.7 (IQR:2.1-7.2) years, 57 patients developed T2DM; the overall incidence rate was 2.8 (95%CI: 2.1 – 3.6) per 1000 person-years of follow up. Exposure to PIs was associated with T2DM (HR: 1.80, 95%CI: 1.04-3.09). In the multivariable analysis, obesity (BMI>30kg/m^2) (aHR=2.26, 95%CI: 1.17-4.36), age >40yrs (aHR=2.16, 95%CI: 1.22-3.83) and male gender, (aHR=2.13, 95%CI: 1.22-3.72) were independently associated with the risk of T2DM. HIV

related factors (baseline CD4 cell count and baseline WHO clinical stage) were not independent risk factors for developing T2DM.

Conclusion

Even though the incidence of T2DM in this HIV cohort was lower than has been observed in other cohorts, our results show that risk factors for developing T2DM among HIV infected people are similar to the general population. HIV-infected patients in sub-Saharan Africa need a comprehensive approach to care that includes better health services for prevention, early detection and treatment of chronic diseases especially among the elderly and obese.

Key words: Type 2 Diabetes mellitus, Zimbabwe, HIV infection

Background

Acess to antiretroviral therapy (ART) has reduced the Human Immunodeficiency Virus (HIV) associated morbidity and mortality among people living with HIV (PLHIV). However, access to long term ART may be associated with toxicities including hyperglycaemia and diabetes mellitus [1]. As PLHIV live longer, they are likely to develop comorbidities such as Type 2 Diabetes Mellitus (T2DM). Furthermore, the prevelance of noncommunicable diseases is increasing in low and middle income countries [2], hence PLHIV in these countries are faced with a dual burden of disease as they grow older. Traditional and well established risk factors of development of T2DM in non HIV infected patients include older age, hypertension, obesity and physical inactivity [3]. Factors associated with the occurrence of T2DM in HIV-infected patients are complex. They include the effects of HIV itself, which is a chronic inflammatory and insulin-resistant condition, genetics, cigarette smoking, physical inactivity, obesity, aging and the toxic effects of ART [4] . As persons infected with HIV are surviving longer due to ART uptake, T2DM and cardiovascular diseases are increasingly noted [5], [6]. The WHO STEPwise chronic disease risk factor surveillance programme (STEPS) quantifies the burden of diabetes in sub-Saharan Africa, which varies widely; it is 6.1% in Cameroon, over 7.1% in Congo, and 10.2% in Zimbabwe [7]. In a recent cross sectional facility based study, 2.1% (95%CI:1.3-3.2%) of people living with HIV in Zimbabwe had cormobid T2DM [8]. Results from the phase 3 HPTN 052 randomised controlled trial done in Uganda and Zimbabwe showed a very low event rate for diabetes mellitus (9 new cases in 1761 patients) among HIV infected patients on ART [9].

There is documented evidence of an increase in the burden of T2DM in Zimbabwe [10]. In 2015, 209,800 cases of diabetes were recorded in the country and these contributed to the national adult prevalence of 2.9% [11]. However, the incidence of T2DM among HIV infected individuals in Zimbabwe is unknown. The increasing burden of non-communicable diseases among PLHIV will increase the costs of comprehensive healthcare provision especially in resource limited settings. Despite this double burden, there is a dearth of

literature surrounding diabetes and HIV research in Zimbabwe. Given the evidence concerning HIV's role (via ART mediated pathways) as a potential risk factor for diabetes, there is a need for this research to be carried out in Zimbabwe. The objective of this study was to assess the incidence and associated risk factors of new onset T2DM in a cohort of HIV infected individuals receiving ART at an outpatient clinic in Zimbabwe.

Methods

Study setting

Newlands Clinic (NC) is a family-centered, nurse-based and doctor supervised HIV treatment center in Harare, Zimbabwe. Nurses provide routine HIV care to patients and doctors consult all patients with new clinical complains and / or abnormal laboratory results. It is a part of the coordinated public-private partnership between the Ministry of Health and Child Care and several private organisations that provide HIV treatment in Zimbabwe. NC provides access to care and treatment to approximately 5,500 HIV-1 infected paediatric, adolescent and adult patients. Patient care follows the Zimbabwe national guidelines [12]. Patients enrolled at NC have similar demographic and socio-economic characteristics to those in the national OI / ART program [13]. NC uses the same guidelines for initiation of ART as the national program. As part of routine HIV care, the following laboratory test are done at least once every year: Full Blood Count (FBC), serum creatinine clearance, liver function tests, CD4 cell count, HIV viral load and urinalysis (since 2013). The clinic does not offer routine testing for lipids and HbA1c.

Study Procedures / Methods

The clinic includes a laboratory and a pharmacy with quick turnaround times for laboratory investigations and convenient drug pick-up after consultations. These services are provided free to patients. All clinic patients are screened for T2DM with random venous blood glucose measurements performed at baseline and routinely once a year by the laboratory.

Diagnosis of T2DM was based on two different criteria defined by the American Diabetes Association [14]. 1) If a patient had an elevated random blood glucose measurement of >11.0 mmol/l, a fasting plasma glucose (FPG) test was done to screen for T2DM. Fasting blood sugar is measured after the patient has not consumed food or drink (except water) for at least 8 hours. If the FPG value was >7.0 mmol/l, the patient was diagnosed with T2DM. 2) Patients who presented with clinical signs and symptoms of hyperglycemia, such as thirst, polyuria, weight loss and blurred vision were screened immediately by measuring random blood sugar; if sugar was elevated (>11.1 mmol/l), they were diagnosed as T2DM. All patients had access to blood sugar measurements. Screening and diagnosis of T2DM is done by a doctor. There has not been any patient diagnosed of type 1 diabetes mellitus at the clinic to date and hence type 1 diabetes mellitus was not part of this analysis. All patient data are entered into an electronic medical record system since the clinic was started in 2004.

Ethical Approval

Newlands Clinic is part of the International epidemiologic Databases to Evaluate AIDS-Southern African Region (IeDEA-SA) [15]. Patients provided written informed consent allowing their clinic data to be used for research analysis to answer epidemiological questions. This study was approved by the Medical Research Council of Zimbabwe (Approval number: MRCZ/A/1336).

Inclusion criteria and definitions

All patients aged 16 years and above at ART commencement receiving care at Newlands Clinic in the period 01 March 2004 to 29 April 2015 were eligible for analysis. Baseline values / variables were at commencement of ART. Patients who were diagnosed with T2DM before or at the time they started ART were excluded from this analysis. Incident T2DM was defined as a documented new diagnosis of T2DM after ART commencement. Hypertension was defined as a documented systolic pressure greater than 140 mm Hg and / or diastolic

pressure greater than 90 mm Hg measured on at least 2 different days or receiving antihypertensive medicines. All patients with a diagnosis of hypertension are on anti-hypertensive medicines such as atenolol, enalapril, spironolactone, amilodipine and antihypertensive medicines are not used for non-hypertensive heart diseases at NC. Baseline values of CD4 and BMI were the closest values, within 3 months before or after start of ART. ART was defined as a regimen of at least three antiretroviral drugs from any drug class. Loss-to-follow-up (LTFU) was defined as failing to attend a scheduled clinic appointment for at least 90 days without documentation of death or transfer to another clinic.

Statistical analysis

The overall and stratified incidence rates of T2DM were calculated as the number of new-onset T2DM cases, divided by the total number of person-years (PY) of follow-up. We calculated T2DM incidence rates for the whole observation period and did not consider interruptions or treatment changes to ART. Data was complete for all variables except baseline BMI where 8.7% (n=357) were missing. We imputed these missing BMI values based on the other characteristics at baseline, and whether the patient developed T2DM or not. Analyses were done for each of the 20 imputed datasets and we used Rubin's rule to combine results [16]. We also did a complete case analysis.

We used crude and adjusted Cox proportional hazards models to describe risk factors for incident T2DM and checked for proportional hazard assumptions using Schoenfold residuals. Use of protease inhibitors (PI) was assessed in the univariable analysis only and not in multivariable analysis because it is in the causal pathway for T2DM. We measured follow-up time from day of ART initiation until the date of T2DM diagnosis, the last follow-up visit, or death, whichever occurred first**.** We considered the following explanatory variables at start of antiretroviral therapy: age (<40 and ≥40 years); gender; baseline CD4 count category (<200 and ≥200 cell/ mm^3); baseline BMI (<30 and ≥30 kg/ m^2, missing baseline BMI data was imputed as a continuous variable); hypertension; and, WHO clinical stage (stages 1

and 2 vs stages 3 and 4). Results are presented as incidence rates per 1000 person years, crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI). All statistical analyses were performed in Stata version 13.0. (StataCorp, College Station, Texas, USA).

Results

Patient characteristics

The Clinic database had 5,467 patient records. We excluded 42 patients who had prevalent T2DM, 6 participants who had not started ART and 1,309 who were children <16 years old. We analysed data for 4,110 patients, of whom 67.2% (n=2,761) were women. The characteristics of the participants at start of ART are shown in Table 1. Median age of participants was 37 years (IQR: 31-43); median baseline CD4 count was 197 cells/mm^3 (IQR: 95-337). Overall 46.6% (n=1,917) participants were in WHO stage 3 or 4. Prevalence of obesity was 9.6% (n=3753). Among the 16% (n=638) patients with hypertension, prevalence of obesity was almost twice as high (30.2%; n=110) when compared to those without hypertension. Median follow-up time for study participants was 4.7 years (IQR 2.1 - 7.2). At the time of data abstraction (29 April 2015), 78% (n= 3,208) participants were still in care, 8.9% (n=364) had died, 5.3% (n=217) were LTFU and 7.8% (n=321) were transferred to other HIV treatment centres.

Incidence of T2DM

The number of new T2DM diagnoses over the 20,504 PY of follow-up was 57; overall incidence rate was 2.8 per 1000 PY (95% CI: 2.1-3.6). There were 5 new T2DM diagnoses among patients who deceased and 4 among patients transferred out. None of the new T2DM diagnoses were diagnosed in pregnancy. The incidence rate of T2DM was higher in men than in women.The incidence rate of T2DM increased with age from 0.48 / 1000 PY (95%CI: 0.07-3.37) among patients younger than 25 years to 8.35 / 1000 PY (95%CI: 5.11-14.32) in those 50 years and above. The incidence rate also increased with an increase in BMI from a rate of 0 /1000 PY in patients with a BMI of < 18 kg/m^2 to a rate of 5.84 / 1000 PY (95%CI: 3.24-10.55) in those who had a BMI of at least 30 kg/ m^2. Hypertensive participants had a higher incidence rate than those without hypertension. We did not see any

196 trend in the incidence of T2DM over the years associated with the change in national ART
197 guidelines. Table 1 higlights the incidence of T2DM for various patient categories. In
198 univariable analysis, patients who had used protease inhibitors were more likely to develop
199 T2DM than those who had not (RR=1.80, 95%CI: 1.04-3.09). Table 2 shows the results of
200 the univariable and multivariable analyses that identified risk factors of diabetes.

201 In the multivariable analysis, men were more likely to develop T2DM than women
202 (aHR=2.13). Patients >40 years old had a higher risk of developing T2DM (aHR=2.16) than
203 patients <40 years old. Obesity (BMI >30 kg/m^2) was an independent risk factor for T2DM
204 (aHR=2.26). HIV-related characteristics (baseline WHO stage and baseline CD4 count) were
205 not associated with risk of developing diabetes. There was no evidence of proportional
206 hazard assumptions violation (p=0.19).

207

208 **Discussion**

209 Overall incidence of T2DM in this cohort of HIV-infected people was 2.8 per 1000 PY of
210 follow-up. The incident rate increased with increases in age and BMI. We identified the
211 following independent risk factors for developing T2DM: Age > 40 years, male gender, and
212 obesity. HIV-related factors (baseline CD4 cell count and baseline WHO clinical stage) were
213 not independent risk factors for the development of T2DM. We did not include use of PIs in
214 the multivariable model because PI use is in the causal pathway for pathogenesis of T2DM
215 and hence cannot be controlled for, however, use of PIs was a significant risk factor in the
216 univariable analysis.

217 We found a much lower T2DM incidence rate than has been reported in other studies. A
218 study from Thailand showed an incidence rate of 5.0 per 1000 PY among patients living with
219 HIV [17]. The Data collection on Adverse events of Anti-HIV Drugs (D.A.D) study showed an
220 incidence rate of 5.7 per 1000 PY [18] and in the Swiss HIV Cohort study the incidence rate
221 was 4.4 per 1000 PY [4]. In a study done in South Africa, Karamchand *et al* found a crude

incidence rate of 13.2 per 1000 PY among HIV infected adults on first-line ART [19]. To the best of our knowledge, there are no studies that have looked at the incidence of T2DM in either HIV positive or negative people in Zimbabwe hence we are not able to compare our findings with national statistics. Several factors might explain the discrepancy between our study results and other studies. The median BMI of 22.3 kg/m^2 among our participants was much lower than, for example, in the Swiss HIV Cohort. We used routinely collected clinic data where patients were screened for T2DM during regular clinic visits and under-reporting is possible. Routine haemoglobin A1C measurements would have better estimated the incidence of T2DM in our cohort, but the incidence of T2DM we found in patients over 40 years of age was still comparable to the findings of both Swiss HIV cohort study and the D.A.D study [4], [18].

This analysis identified key risk factors for the development of T2DM among patients living with HIV. These risk factors are similar to those identified among the general population and are also consistent with findings from other cohort studies [4], [18]. Not surprisingly, the incidence rate increased with age and was highest in the patients above 50 years of age, highlighting the increased burden of health problems among individuals who are ageing with HIV. Our findings of an increased risk of T2DM with increasing age and BMI are consistent with findings from studies that have looked at risk factors of T2DM among both HIV positive and HIV negative individuals [20]. As in people not infected with HIV, age is an important risk factor for both T2DM and cardiovascular diseases. Since aging cannot be avoided, it is important to regularly screen the elderly for diseases such as diabetes. While studies have demonstrated a lower BMI in HIV-infected patients with diabetes compared to non-infected matched cohorts [21], the association between T2DM and obesity persists in HIV infected patients. For example, Galli *et al.* found that the prevalence of T2DM in those with normal BMI was 3.2% in HIV patients and 1.1% in HIV uninfected. However, in the overweight and obese categories, T2DM prevalence rose to 3.9% and 12.7% among HIV infected patients compared with 3.1% and 7.8% respectively in HIV-uninfected patients [22]. HIV treatment

programs should educate patients on the dangers of obesity so as to minimise the risk of developing T2DM. Furthermore, elderly PLHIV should be educated on the association of ageing and the risk of developing T2DM. In the univariable analysis, our results showed that patients who had used PIs (ritonovir boosted atazanavir and / or lopinavir) were 1.8 times more likely to develop new-onset T2DM. These findings are consistent with other studies that have demonstrated the association between PI use and metabolic complications such as T2DM [20], [23]. Use of ART medicines has increasingly become important as a potential risk factor for T2DM. In a review article on diabetes and HIV, Murphy and Gerard report that PLHIV following treatment with some first generation ART drug classes (protease inhibitors) had higher rates of diabetes incidence compared to HIV negative participants [24]. In South Africa, it was recently reported that treatment with efavirenz, as well as stavudine and zidovudine, increased the risk of incident diabetes [25]. In this cohort, we could not assess the association between efavirenz or nevirapine with T2DM because efavirenz became available only a year ago and before that all patients received nevirapine as part of their first line ART regimen. We could also not assess the associations of different PIs because Patients have received both Lopinavir and Atazanavir at different times depending on which drug was available and the recording of different PIs was not very accurate.

We identified hypertension as being associated with developing T2DM, however, this association was not significant in the multivariable analysis. We did not assess the possible effects of the antihypertensive medicines on the risk of developing T2DM. The high burden of hypertension in this cohort illustrates the increasing burden of non-communicable diseases (NCDs) among HIV infected adults. NCDs collectively contribute to the decreased life expectancy of HIV-infected patients on treatment. Furthermore, treatment of co-morbidities among PLHIV increases the pill burden and this may in turn affect adherence to medicines [26]. Men were more likely to develop T2DM in this cohort. This finding is inconsistent with global estimates that indicate that sex has little effect on diabetes. Sex distribution among diabetic patients varies widely in sub-Saharan Africa, with no discernable

trend [27]. Our study did not show any association between baseline CD4 cell count and WHO clinical stage with the risk of developing T2DM. However, other studies have found an increased risk of T2DM with lower CD4 cell count and longer duration of HIV infection. Furthermore, studies have found associatiojns between high HIV viral load and diabets [22], [28].

The major strength of our study was that patient characteristics are typical for many clinics in sub-Saharan Africa [29], so our results are likely to accurately reflect routine clinical care in the region. Our LTFU rate was lower than in other clinics [30], [31], hence our results were less affected by patient dropouts. Because the clinic uses an electronic record system with a rigorous data quality control system, our data was complete for all variables except baseline BMI; results were similar with and without imputing missing BMI.

Our study had several limitations, chiefly because we used routine clinic data. Limitations included a lack of population based samples, absence of HIV negative, HIV positive and ART naïve comparison groups and incomplete measurement of key T2DM risk factors such as nutrition and physical exercise. The number of new-onset T2DM in our cohort was very low and this in turn limited the power of our study. In our analysis, we could not control for possible time dependent confounding because of unavailability of complete follow up data. Since all participants were enrolled at a single urban site, this may reduce the generalizability of our findings to the population of Zimbabwe and beyond.

Conclusion

Even though the incidence of T2DM in this HIV cohort was lower than has been observed in other cohorts, our results show that T2DM is a problem as the population of HIV-infected patients continues to age. HIV-infected patients in sub-Saharan Africa need more than ART; they need a comprehensive approach to care that includes better health services for prevention, early detection and treatment of chronic diseases.

Competing Interest

The authors have no competing interests to declare.

Acknowledgements

The authors acknowledge Kali Tal and Ruedi Luethy for their editorial and clinical comments. Research reported in this publication was supported by National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number U01AI069924 (PI: Egger and Davies). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. O Keiser was supported by a professorship grant from the Swiss National Science Foundation (grant# 163878).

Authors' Contributions

CC wrote the first draft of the study protocol. All authors contributed to the final version of the protocol. CC and TS did the statistical analyses, with interpretation of results by CC and OK. CC wrote the first draft of the report which was revised by OK, CM, BK, ME and BB. All authors revised and approved the final version for submission.

Table 1: Participant baseline and clinical characteristics

	Variable	Patients (N)	Person years at risk	Diabetes cases	Incidence Rate/1000 pyrs (95% CI)
Sex	**Female**	2,761	14,178	30	2.12 (1.48-3.03)
	Male	1,349	6,326	27	4.27 (2.93-6.22)
Age (years)	**<25**	491	2,105	1	0.48 (0.07-3.37)
	≥25-<40	2,149	11,068	21	1.81 (1.17-2.80)
	≥40-<50	954	5,111	19	3.72 (2.37-5.83)
	≥50	402	1,916	16	8.35 (5.11-14.32)
***BMI (kg/m^2)**	**<18**	429	2,006	0	
	≥18-<24	1,962	10,037	22	2.19 (1.44-3.33)
	>24-<30	998	5,486	22	4.01 (2.64-6.09)
	≥30	364	1,882	11	5.84 (3.24-10.55)
WHO STAGE	**1/2**	2,193	10,462	31	2.96 (2.08-4.21)
	3/4	1,917	10,041	26	2.59 (1.76-3.80)
CD4 Count (cell/µl)	**<200**	2,083	10,571	31	2.93 (2.06-4.17)
	≥200	2,027	9,933	26	2.62 (1.78-3.84)
Hypertension	**Yes**	638	4170	24	5.75 (3.86-5.89)
	No	3,472	16,333	33	2.02 (1.44-2.84)
PI Use	**Yes**	734	4,750	20	4.22 (2.72-6.53)
	No	3,376	15,759	37	2.35 (1.70-2.24)
NVP Use	**Yes**	2,934	16,443	49	2.98 (2.25-3.94)
	No	1,176	4,067	8	1.97 (0.99-3.94)
EFV Use	**Yes**	846	2,037	3	1.47 (0.47-4.57)
	No	3,264	18,466	54	2.92 (2.24-3.82)

BMI=Body Mass Index; T2DM= diabetes mellitus; CI= confidence intervals,PI = Protease Inhibitor; NVP=Nevirapine; EFV=Efavirenz; WHO= World Health Organisation

336 **Table 2: Factors associated with new-onset T2DM among HIV infected patients**

	Univariable Analysis		Multivariable Analysis (based on multiple imputation)		Multivariable Analysis (complete case analysis; n=3 753)	
Characteristics	**HR (95% CI)**	**P**	**aHR (95 CI)**	**P**	**aHR (95 CI)**	**P**
Male gender	2.01 (1.20-3.40)	0.040	2.13 (1.22- 3.72)	0.01	2.31 (1.30- 4.13)	0.004
Age > 40yrs	3.08 (1.80-5.28)	0.001	2.16 (1.22-3.83)	0.01	2.32 (1.29-4.16)	0.005
WHO stage 3/4	0.84 (0.52-1.47)	0.611	0.76 (0.44-1.31)	0.32	0.76 (0.44-1.33)	0.34
BMI > 30 kg/m2	2.33 (1.20-4.50)	0.010	2.26 (1.17-4.36)	0.01	3.10 (1.51-6.36)	0.002
CD4<200 cells/µl	0.89 (0.53-1.50)	0.220	0.67 (0.38-1.18)	0.17	0.73 (0.41-1.30)	0.28
Hypertension	3.94 (2.34-6.65)	0.000	1.79 (1.02-3.12)	0.04	1.60 (0.91-2.84)	0.11
PI use	1.80 (1.04-3.09)	0.032	-	-	-	-

337 Hypertension= Receiving antihypertensive medication or documented diagnosis of hypertension; BMI=Body Mass
338 Index; aHR = adjusted Hazard ratios, PI=Protease Inhibitor, PI use excluded from multivariable analysis because
339 it is the causal pathway for T2DM

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